HETEROCYCLES, Vol. 72, 2007, pp. 553 - 565. © The Japan Institute of Heterocyclic Chemistry
Received, 19th December, 2006, Accepted, 18th January, 2007, Published online, 19th January, 2007. COM-06-S(K)48

# EFFICIENT SYNTHESIS OF SUBSTITUTED 3-AMINO-3,4-DIHYDROPYRAN-2-ONES
# DIASTEREO AND ENANTIOSELECTIVE TANDEM MICHAEL ADDITION AND LACTONIZATION BETWEEN α,β-UNSATURATED KETONES AND GLYCINE-DERIVED SILYL ENOLATES USING A CHIRAL QUATERNARY AMMONIUM PHENOXIDE

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*Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday*

**Abstract** – Chiral quaternary ammonium phenoxides are readily prepared from commercially available cinchona alkaloids and are employed as useful new asymmetric organocatalysts. The cinchonidine-derived catalyst is highly effective on Michael addition and successive lactonization between glycine-derived silyl enolates and *α,β*-unsaturated ketones. According to this asymmetric reaction, the corresponding 3-amino-3,4-dihydropyran-2-ones are formed in high yields with complete diastereoselectivities and excellent enantioselectivities.

## INTRODUCTION

3,4-Dihydropyran-2-one derivatives are often used as useful synthetic intermediates for the preparations of 2-pyranones,[1] *γ*-lactones,[2] cyclic enamines,[3] and so on. In the conventional methods, the above derivatives were prepared by the Michael addition of the enolates such as silyl enol ethers [4a–4c] or lithiated

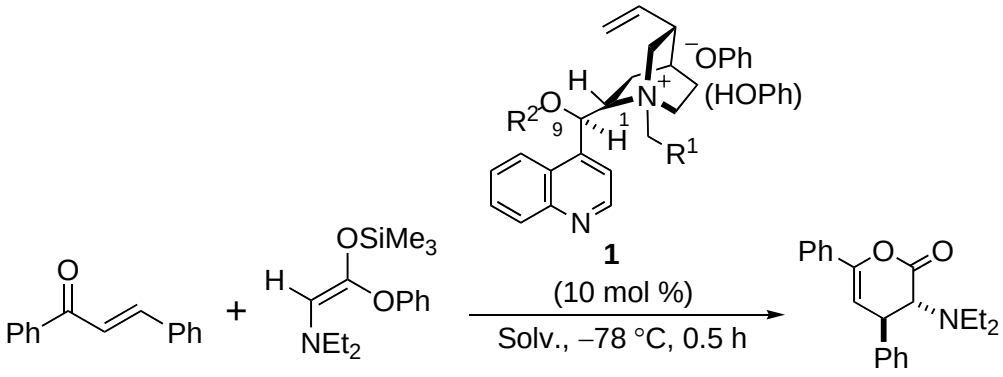
*N*-acylbenzotriazoles[4d] to $\alpha,\beta$-unsaturated ketones. However, these preparative methods of using substituted 3,4-dihydropyran-2-ones were limited to the derivatives having alkyl substituents at 3-position. Recently, the novel types of chiral quaternary ammonium phenoxides were shown to be prepared from commercially available cinchona alkaloids and the phenoxides were employed there as useful new asymmetric catalysts.[5] The cinchonidine-derived catalyst possessing both a sterically hindered *N*(1)-9-anthracenylmethyl group and a strongly electron-withdrawing C(9)-*O*-3,5-bis(trifluoromethyl) benzyl group was effectively used in tandem Michael addition and successive lactonization between silyl enolates and $\alpha,\beta$-unsaturated ketones, which afforded 3-alkyl-3,4-dihydropyran-2-ones in high yields with high diastereo- and enantio-selectivities.[5b] In this catalytic system, the phenoxy group contained in the silyl enolate behaves as an effective leaving group to facilitate intramolecular cyclization of the Michael-adduct intermediate as well as the liberated phenoxide ion that worked well for promotion of this reaction. In this paper, we would like to describe in detail our studies on highly selective synthesis of 3-amino-3,4-dihydropyran-2-ones. These dihydropyranones are considered quite useful precursors of the $\alpha$-amino acids in tandem Michael addition and lactonization between silyl enolates derived from glycine phenyl ester and $\alpha,\beta$-unsaturated ketones using a catalytic amount of cinchonidine-derived quaternary ammonium phenoxides.

## RESULTS AND DISCUSSION

In the first place, reactions of chalcone **2a** with trimethylsilyl (TMS) enolate **3a** derived from glycine phenyl ester[6] were tried at –78 °C for 0.5 h in the presence of 10 mol % of several cinchonidine-derived quaternary ammonium phenoxides[7,8] in order to examine the effect of the catalysts (Table 1). When *N*-arylmethylated cinchonidinium phenoxides **1a–1c** having a hydroxyl group were used, 3-diethylamino-3,4-dihydropyran-2-one **4a** was afforded in excellent *trans*-selectivity (*trans/cis* = >99:1) with low enantioselectivity (Entries 1–6). It is particularly interesting that the use of a catalyst having bulky substituents on the nitrogen atom of cinchonidine, **1b** ($R^1$ = 3,5-bis(3,5-di-tert-butylphenyl)phenyl or **1c** ($R^1$ = 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl), gave the opposite enantioselectivity in THF to that observed in the reaction with **1a** (Entries 3, 5). Though the detailed mechanism has not yet been made clear from these observations, it indicated that the substituents on nitrogen atom of cinchonidine-derived catalyst played an important role in controlling the absolute stereochemistry of the two newly created chiral carbon centers in this asymmetric tandem reaction. Cinchonidine-derived catalyst **1d** possessing both a sterically hindered *N*(1)-9-anthracenylmethyl group and a strongly electron -withdrawing C(9)-*O*-3,5-bis(trifluoromethyl)benzyl group was thus employed in tandem Michael

addition and successive lactonization in THF, which afforded 3-diethylamino-3,4- dihydropyran-2-one **4a** in 96% yield with excellent *trans*-selectivity (*trans/cis* = >99:1) while the enantioselectivity stayed moderate (78% ee) (Entry 7). Further, the enantioselectivity increased up to 92% ee when the reactions were carried out in $CH_2Cl_2$ (Entry 8). In addition, the dihydropyranone **4a** was obtained in 93% yield with 93% ee when the amount of the catalyst was reduced to 5mol % (Entry 9).

**Table 1.** Effects of Catalysts




**2a** **3a** (1.6 equiv.) (+)-**4a**

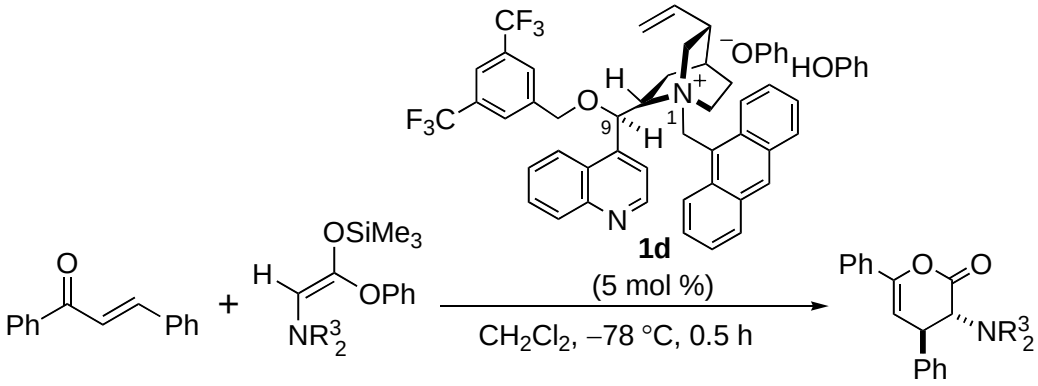
| Entry | Catalyst | | Solvent | Yield/%[a] (*trans/cis*)[b] | % ee[c] |
|---|---|---|---|---|---|
| 1 | **1a:** $R^1$ = 2,6-$F_2C_6H_3$ | $R^2$ = H | THF | 72 (>99:1) | 18 |
| 2 | **1a:** $R^1$ = 2,6-$F_2C_6H_3$ | $R^2$ = H | $CH_2Cl_2$ | 48 (>99:1) | 34 |
| 3 | **1b:** $R^1$ = 3,5-[3,5-(*t*-Bu)$_2C_6H_3$]$_2C_6H_3$ | $R^2$ = H | THF | 60 (>99:1) | 14[f] |
| 4 | **1b:** $R^1$ = 3,5-[3,5-(*t*-Bu)$_2C_6H_3$]$_2C_6H_3$ | $R^2$ = H | $CH_2Cl_2$ | 72 (>99:1) | 44 |
| 5 | **1c:** $R^1$ = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$ | $R^2$ = H | THF | 66 (>99:1) | 29[f] |
| 6 | **1c:** $R^1$ = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$ | $R^2$ = H | $CH_2Cl_2$ | 27 (>99:1) | 11[f] |
| 7 | **1d:** $R^1$ = 9-Anthracenyl | $R^2$ = 3,5-$(CF_3)_2C_6H_3CH_2$ | THF | 96 (>99:1) | 78 |
| 8 | **1d:** $R^1$ = 9-Anthracenyl | $R^2$ = 3,5-$(CF_3)_2C_6H_3CH_2$ | $CH_2Cl_2$ | 96 (>99:1) | 92 |
| 9[d] | **1d:** $R^1$ = 9-Anthracenyl | $R^2$ = 3,5-$(CF_3)_2C_6H_3CH_2$ | $CH_2Cl_2$ | 93 (>99:1) | 93 |
| 10[e] | **1d:** $R^1$ = 9-Anthracenyl | $R^2$ = 3,5-$(CF_3)_2C_6H_3CH_2$ | $CH_2Cl_2$ | 17 (>99:1) | 90 |

[a]Isolated yield. [b]Diastereomeric ratio was determined by $^1$H-NMR analysis. [c]Enantiomeric excess of major *trans*-**4** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (volume ratio = 60/1) as a solvent. [d]Catalyst (5mol %) was used. [e]Catalyst (3mol %) was used. [f]Opposite enantiomer (–)-**4a** was obtained.

In order to examine the effect of alkyl substituents ($R^3$) of the nitrogen of TMS enolates (Table 2), reactions of chalcone **2a** with several trimethylsilyl (TMS) enolates **3b**–**3d** derived from glycine phenyl

ester were next tried at –78 °C for 0.5 h in the presence of 5 mol % of cinchonidine-derived quaternary ammonium phenoxide **1d**. A reaction of sterically-hindered glycine-derived TMS enolate such as **3b** ($R^3$ = *i*-Pr) gave the 3-amino-3,4-dihydropyran-2-one in lower enantioselectivity (Entry 1) whereas the use of TMS enolate having a cyclic amine (**3c**) gave high diastereo- and enantioselectivities (*trans/cis* = 98:2 *trans* = 93% ee) (Entry 2). Further, the reaction of TMS enolate having a diallylamino group (**3d**), in which deprotection of the allyl group was readily carried out by using palladium(0) [9] or rhodium(I) [10] via isomerization, afforded the corresponding dihydropyranone in excellent yield with almost complete stereochemical control (*trans/cis* = >99:1 *trans* = 92% ee) (Entry 3).

**Table 2.** Reactions of chalcone **2a** with various glycine-derived silyl enolates **3** in the presence of catalyst **1d**



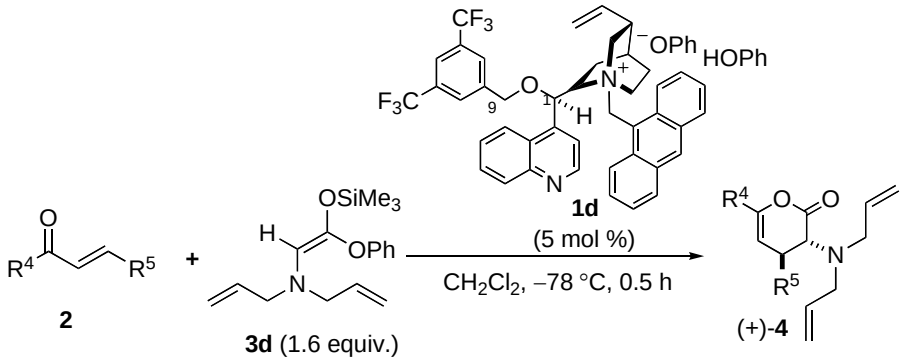

**2a** **3** (1.6 equiv.) (+)-**4**

| Entry | Silyl enolate | Product | Yield/%[a] | *trans*/cis[b] | % ee[c] |
|---|---|---|---|---|---|
| 1 | **3b:** $R^3$ = *i*-Pr | **4b** | 99 | 97:3 | 77 |
| 2 | **3c:** $R^3$ = $-(CH_2)_5^-$ | **4c** | 92 | 98:2 | 93 |
| 3 | **3d:** $R^3$ = allyl | **4d** | 99 | >99:1 | 92 |

[a]Isolated yield. [b]Diastereomeric ratio was determined by $^1$H-NMR analysis. [c]Enantiomeric excess of major *trans*-**4** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H or Chiralpak AD-H) with hexane/2-propanol (volume ratio = 60/1) as a solvent.

Next, reactions of TMS enolate **3d** with various $\alpha,\beta$-unsaturated ketones **2**[11] were tried in the presence of 5 mol % cinchonidine-derived catalysts **1d** in $CH_2Cl_2$ at –78 °C for 0.5 h (Table 3). $\alpha,\beta$-Unsaturated ketones **2** with electron withdrawing– or donating– group reacted smoothly to afford the corresponding 3-diallylamino-3,4-dihydropyran-2-ones (**4**) in high yields with complete diastereoselectivities and excellent enantioselectivities (Entries 1–8). When alkyl-substitued $\alpha,\beta$-unsaturated ketone **2** was used, 3,4-dihydropyran-2-one **4m** was afforded with moderate enantioselectivity (Entry 9).

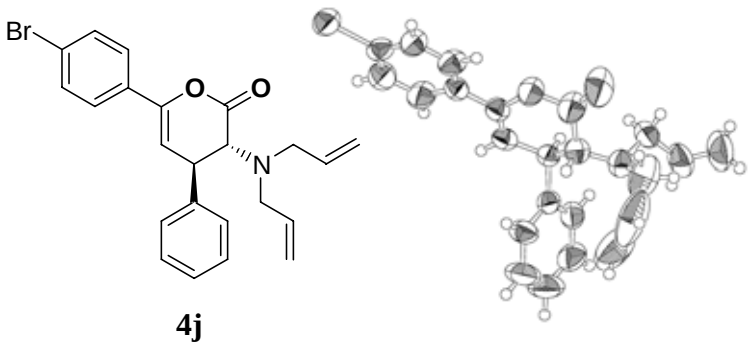
**Table 3.** Diastereo- and enantioselective synthesis of 3-(diallylamino)-3,4-dihydropyran-2-ones by using catalyst **1d**




| Entry | $R^4$ | $R^5$ | Product | Yield/%[a] (*trans*/cis)[b] | % ee[c] |
|---|---|---|---|---|---|
| 1 | Ph | 4-(MeO)$C_6H_4$ | **4e** | 99 (99:1) | 94 |
| 2 | 4-(MeO)$C_6H_4$ | Ph | **4f** | 99 (>99:1) | 96 |
| 3 | Ph | 4-F$C_6H_4$ | **4g** | 98 (>99:1) | 92 |
| 4 | 4-F$C_6H_4$ | Ph | **4h** | 96 (99:1) | 94 |
| 5 | Ph | 4-Br$C_6H_4$ | **4i** | 99 (>99:1) | 92 |
| 6 | 4-Br$C_6H_4$ | Ph | **4j** | 99 (>99:1) | 92 |
| 7 | 4-(MeO)$C_6H_4$ | 4-Br$C_6H_4$ | **4k** | 98 (>99:1) | 97 |
| 8 | 4-Br$C_6H_4$ | 4-(MeO)$C_6H_4$ | **4l** | 97 (>99:1) | 94 |
| 9 | Ph | Me | **4m** | 72 (>99:1) | 67 |
| 10 | PhCH=CH | Ph | **4n** | 95 (>99:1) | 87 |

[a]Isolated yield. [b]Diastereomeric ratio was determined by $^1$H-NMR analysis. [c]Enantiomeric excess of major *trans*-**4** was determined by HPLC analysis using a chiralcolumn (DAICEL Chiralcel OD-H or Chiralpak AD-H) with hexane/ 2-propanol (volume ratio= 60/1) as a solvent.

Relative and absolute configurations at the two newly created adjacent carbon centers of **4k** were identified definitely by X-ray crystallographic analysis (Figure 1).[12] It was indicated there that the (3*R*,4*R*)-3-(diallylamino)-4,6-diphenyl-3,4-dihydropyran-2-one obtained by way of tandem Michael




**4j**

**Figure 1.** ORTEP drawing of compound **4j**.

addition and lactonization had the same configuration to those of non-naturally occurring D-amino acids. A plausible reaction mechanism[13] may be explained as shown in Figure 2: that is, the phenoxy group of glycine-derived silyl enolate is located at the position of π–π stacking interaction with 9-anthracenyl part of the quaternary ammonium catalyst. Pentacoordinated hypervalent silicate[14] is electrostatically stabilized by $N^+$ of the catalyst. The *α,β*-unsaturated ketone interacts with a quinoline part of the catalyst through the π–π stacking and the carbonyl oxygen comes close to $N^+$ of the catalyst by electrostatic interaction. This proposed mechanism is compatible with the above experimental results.

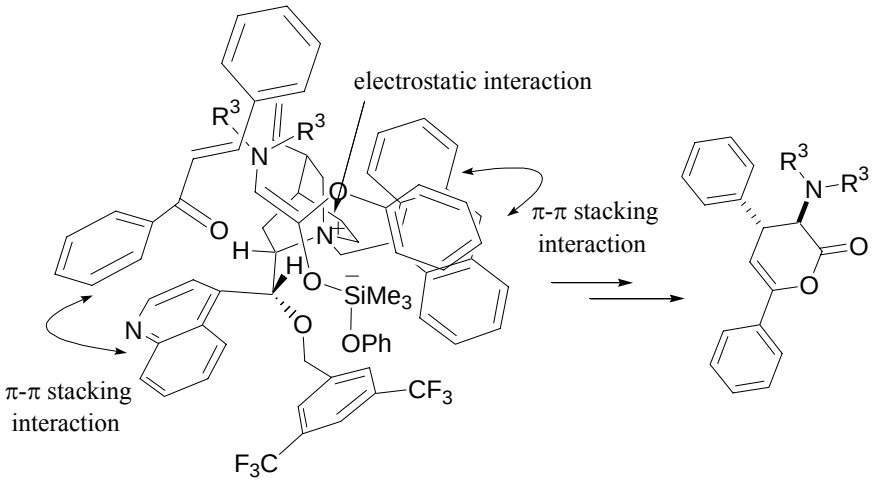



**Figure 2.** Plausible Reaction Mechanism

In conclusion, an efficient method for the synthesis of optically active 3-amino-3,4-dihydropyran-2-ones was established via asymmetric tandem Michael addition and lactonization between various glycine-derived silyl enolates and *α,β*-unsaturated ketones by using a catalytic amount of cinchona alkaloid-derived chiral quaternary ammonium phenoxide **1d** as a Lewis base. This method effectively provides a variety of 3-amino-3,4-dihydropyran-2-ones with excellent stereochemical control in high yield. Further studies on using chiral quaternary ammonium phenoxides in other catalytic asymmetric reactions, particularly in the case of organosilicon reagents, are now in progress.

## EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus (Yanaco MP-S3) and remain uncorrected. Infrared (IR) spectra were recorded by an attenuated total reflection (ATR) method on a SensIR Technologies Travel *IR*$^{TM}$ Portable FT-IR spectrometer. $^1$H NMR spectra were recorded on a JEOL JNM-EX270L (270 MHz) spectrometer; chemical shifts ($\delta$) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet;

m, multiplet; br, broad. $^{13}$C NMR spectra were recorded on a JEOL JNM-EX270L (68 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; $\delta$ = 77.0 ppm, $CD_3OD$; $\delta$ = 49.0 ppm). High-resolution mass spectra (HRMS) were recorded on a JMS-SX102A mass spectrometer or LCT premier. Elemental analyses were conducted using a Yanaco MT-5 CHN corder. X-ray crystallographic analysis was under taken using a Rigaku AFC-5S diffractometer with graphite-monochromated Mo-K$\alpha$ radiation. Analytical high-performance liquid chromatography (HPLC) was performed on a Hitachi LC-Organizer, L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator. Enantiomeric excess (ee) was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H or Chiralpak AD-H, $\phi$4.6 $\times$ 250 mm) with hexane/2-propanol as a solvent. Analytical TLC was performed on Merck preparative TLC plates (silica gel 60 GF254, 0.25 mm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. All reagents were purchased from Tokyo Kasei Kogyo, Kanto Chemical, Kokusan Chemical, Wako Pure Chemical Industries, or Aldrich Chemical. All glycine-derived silyl enolates **3** were prepared from the corresponding phenyl carboxylates by using known methods.[6] Cinchonidine-derived chiral quaternary ammonium phenoxides were prepared according to the reported procedures.[8]

**Cinchonidine-derived catalyst (1a) [$R^1$ = 2,6-$F_2C_6H_3$, $R^2$ = H]**

Pale yellow powder; $[\alpha]_D^{19}$ = +88.0 ° (*c* = 0.10 in $CHCl_3$, 93% ee); mp 131–133 °C (decomp); IR (ATR): $\nu$ = 3056, 1627, 1585, 1472, 1268, 1240, 1163; $^1$H NMR ($CD_3OD$): $\delta$ = 8.93 (d, *J* = 4.6 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.97–7.80 (m, 1H), 7.79–7.66 (m, 3H), 7.28 (t, *J* = 8.7 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 6.67–6.64 (m, 3H), 6.57 (t, *J* = 7.3 Hz, 1H), 5.76–5.63 (m, 1H), 5.33 (d, *J* = 12.8 Hz, 1H), 5.13–4.85 (m, 4H), 4.62–4.43 (m, 1H), 4.16–4.02 (m, 1H), 3.63–3.54 (m, 2H), 3.39–3.20 (m, 1H), 2.81–2.66 (m, 1H), 2.34–2.18 (m, 2H), 2.05 (br s, 1H), 1.96–1.79 (m, 1H), 1.47–1.34 (m, 1H); $^{13}$C NMR ($CD_3OD$): $\delta$ = 165.3, 163.1, 161.7, 150.9, 148.6, 147.4, 138.5, 131.0, 130.3, 130.0, 129.2, 126.0, 123.8, 121.3, 118.0, 117.5, 117.5, 113.7, 113.4, 106.0, 70.0, 66.5, 62.4, 53.3, 53.0, 39.4, 27.6, 26.1, 22.6. HRMS ($FAB^+$) calcd for $[C_{26}H_{27}F_2N_2O]^+$ 421.2091, found *m*/*z* 421.2074.

**(*E*) *N,N*'-Diethyl-2-phenoxy-2-trimethylsilyloxyetenamine (3a)**

Colorless oil; IR (ATR): $\nu$ = 2968, 1698, 1596, 1492, 1252, 1220, 1201, 1161 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 7.29–7.22 (m, 2H), 7.03–6.95 (m, 3H), 4.62 (s, 1H), 2.66 (q, *J* = 7.1 Hz, 4H), 1.03 (t, *J* = 7.1 Hz, 6H), 0.13 (s, 9H); $^{13}$C NMR ($CDCl_3$): $\delta$ = 155.0, 146.3, 128.9, 122.0, 116.9, 106.8, 47.8, 13.0, -0.2.

**(*E*) *N,N*'-Diisopropyl-2-phenoxy-2-trimethylsilyloxyetenamine (3b)**

Colorless oil; IR (ATR): ν = 2965, 1776, 1595, 1492, 1251, 1195, 1162, 1119 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.29–7.21 (m, 2H), 7.03–6.94 (m, 3H), 4.78 (s, 1H), 3.21–3.04 (m, *J* = 7.1 Hz, 4H), 1.03 (d, *J* = 6.4 Hz, 12H), 0.15 (s, 9H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 154.8, 147.8, 128.4, 121.5, 117.0, 100.1, 49.5, 20.5, -0.4.

***N*-[(*E*)-2-Phenoxy-2-trimethylsilanyloxy-vinyl]piperidine (3c)**

Pale yellow oil; IR (ATR): ν = 2934, 1595, 1492, 1251, 1197, 1161, 1120 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.30–7.23 (m, 2H), 7.04–6.96 (m, 3H), 4.89 (s, 1H), 2.73–2.38 (m, 4H), 1.57–1.18 (m, 6H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 156.6, 142.3, 129.1, 128.8, 118.8, 116.3, 110.3, 57.6, 25.5, 24.0, -0.4.

**(*E*) *N,N'*-Diallyl-2-phenoxy-2-trimethylsilyloxyetenamine (3d)**

Pale yellow oil; IR (ATR): ν = 2961, 1595, 1491, 1252, 1197, 1161 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.40–7.33 (m, 2H), 7.14–7.07 (m, 3H), 5.99–5.84 (m, 2H), 5.24–5.16 (m, 4H), 4.96 (s, 1H), 3.40 (d, *J* = 6.4 Hz, 4H), 0.22 (s, 9H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 155.0, 144.4, 135.6, 128.9, 122.0, 124.4, 116.8, 116.7, 57.6, -0.2.

**A typical experimental procedure for the synthesis of optically active 3-amino-3,4-dihydropyran-2-ones 4 by using cinchonidine-derived catalyst 1d (Table 1, Entry 9)**

To a stirred solution of cinchonidine-derived catalyst **1d** (13.5 mg, 0.015 mmol) in $CH_2Cl_2$ (1.0 mL) were successively added a solution of chalcone **2a** (62.5 mg, 0.3 mmol) in $CH_2Cl_2$ (0.8 mL) and a solution of trimethylsilyl enolate **3a** (113 mg, 0.48 mmol) in $CH_2Cl_2$ (0.8 mL) at –78 °C. After the mixture was stirred for 0.5 h at the same temperature, it was quenched with saturated aqueous $NH_4Cl$ solution and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated. The crude product was purified by PTLC (hexane/EtOAc = 6/1) to give the corresponding **4a** (93.0 mg, 96% yield). The enantiomeric excess of the product was determined by HPLC analysis (93% ee) as a colorless crystal.

***trans*-3-(Diethylamino)-4,6-diphenyl-3,4-dihydropyran-2-one (4a)**

Colorless crystals; $[\alpha]_D^{19}$ = +101 ° (*c* = 0.50 in $CHCl_3$, 93% ee); mp 96–99 °C; IR (ATR): ν = 2972, 1757, 1450, 1276, 1244, 1214, 1164, 1137, 1106, 1082, 1071, 1017 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.65–7.61 (m, 2H), 7.40–7.25 (m, 8H), 5.80 (d, *J* = 2.7 Hz, 1H), 3.94 (dd, *J* = 11.4 Hz, 2.7 Hz, 1H), 3.77 (d, *J* = 11.4 Hz, 1H), 2.90–2.77 (m, 2H), 2.73–2.60 (m, 2H), 0.83 (t, *J* = 7.1 Hz, 6H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 167.9, 148.4, 141.9, 132.0, 128.9, 128.4, 128.2, 128.0, 127.0, 124.4, 104.8, 64.4, 45.0, 42.9, 14.4; Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.19; H, 7.37; N, 4.21; HPLC

analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 9.6 min (major) and 12.3 min (minor).

***trans*-3-(Diisopropylamino)-4,6-diphenyl-3,4-dihydropyran-2-one (4b)**

Colorless crystals; $[\alpha]_D^{20}$ = +82 ° (*c* = 0.50 in $CHCl_3$, 77% ee); mp 117–119 °C; IR (ATR): ν = 2961, 1756, 1498, 1453, 1363, 1281, 1226, 1182, 1157, 1113, 1084, 1031 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.66–7.62 (m, 2H), 7.39–7.24 (m, 8H), 5.77 (d, *J* = 2.5 Hz, 1H), 3.95 –3.87 (m, 2H), 3.21–3.11 (m, 2H), 1.15 (d, *J* = 6.6 Hz, 6H), 0.68 (d, *J* = 6.8 Hz, 6H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 170.8, 148.0, 142.3, 132.1, 128.8, 128.7, 128.4, 128.2, 127.1, 124.5, 105.1, 60.6, 46.6, 44.8, 23.9, 21.5; Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.86; H, 7.95; N, 3.88; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 8.4 min (major) and 9.5 min (minor).

***trans*-4,6-Diphenyl-3-piperidino-3,4-dihydropyran-2-one (4c)**

Colorless crystals; $[\alpha]_D^{22}$ = +168 ° (*c* = 0.50 in $CHCl_3$, 93% ee); mp 100–101 °C; IR (ATR): ν = 2934, 1758, 1494, 1449, 1277, 1251, 1138, 1116, 1101, 1029, 1020 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.67–7.63 (m, 2H), 7.43–7.24 (m, 8H), 5.84 (d, *J* = 4.0 Hz, 1H), 4.02–3.66 (m, 1H), 4.13 (d, *J* = 7.1 Hz, 1H), 2.91–2.84 (m, 2H), 2.61–2.55 (m, 2H), 1.57–1.26 (m, 6H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 166.1, 148.6, 141.4, 132.0, 128.9, 128.5, 128.3, 127.5, 127.0, 124.5, 104.0, 68.6, 50.4, 42.2, 26.4, 24.2; Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.29; H, 7.21; N, 4.16; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 22.8 min (minor) and 23.9 min (major).

***trans*-3-(Diallylamino)-4,6-diphenyl-3,4-dihydropyran-2-one (4d)**

Colorless crystals; $[\alpha]_D^{22}$ = +38 ° (*c* = 0.50 in $CHCl_3$, 92% ee); mp 136–137 °C; IR (ATR): ν = 2846, 1751, 1494, 1452, 1278, 1247, 1149, 1106, 1033, 1021 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.64–7.60 (m, 2H), 7.41–7.22 (m, 8H), 5.84 (d, *J* = 2.2 Hz, 1H), 5.47–5.34 (m, 2H), 5.05–4.96 (m, 4H), 3.99 (dd, *J* = 12.5 Hz, 2.2 Hz, 1H), 3.88 (d, *J* = 12.5 Hz, 1H), 3.49–3.30 (m, 4H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 167.9, 148.4, 141.4, 135.0, 131.8, 129.4, 129.0, 128.4, 128.3, 128.2, 127.1, 124.5, 117.0, 105.0, 62.8, 53.5, 42.6; Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.78; H, 6.88; N, 4.05; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 9.6 min (major) and 12.3 min (minor).

***trans*-3-(Diallylamino)-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydropyran-2-one (4e)**

Colorless crystals; $[\alpha]_D^{22}$ = +31 ° (*c* = 0.50 in $CHCl_3$, 94% ee); mp 44–47 °C; IR (ATR): ν = 2834, 1769, 1511, 1445, 1244, 1177, 1132, 1105, 1037, 1018 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.64–7.60 (m, 2H),

7.38–7.34 (m, 3H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 5.76 (d, *J* = 2.3 Hz, 1H), 5.52–5.37 (m, 2H), 5.07–4.97 (m, 3H), 3.98 (dd, *J* = 12.6 Hz, 2.3 Hz, 1H), 3.86–3.81 (m, 5H), 3.47–3.30 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ = 167.9, 158.5, 148.1, 136.2, 133.4, 131.8, 129.1, 128.8, 128.3, 124.4, 116.8, 113.5, 105.3 62.8, 55.2, 53.4, 41.6; Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.41; H, 6.87; N, 3.77; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 8.5 min (major) and 12.8 min (minor).

***trans*-3-(Diallylamino)-6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyran-2-one (4f)**

Colorless oil; $[\alpha]_D^{19}$ = +29 ° (*c* = 0.50 in $CHCl_3$, 96% ee); IR (ATR): ν = 2838, 1761, 1607, 1511, 1453, 1247, 1177, 1137, 1108, 1028 cm$^{-1}$; $^1$H NMR ($CDCl_3$): 7.55 (d, *J* = 8.9 Hz, 2H), 7.41–7.20 (m, 5H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.64 (d, *J* = 2.3 Hz, 1H), 5.51–5.36 (m, 2H), 5.06–4.96 (m, 4H), 3.96 (dd, *J* = 12.4 Hz, 2.3 Hz, 1H), 3.90–3.82 (m, 5H), 3.47–3.29 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ =168.0, 160.0, 148.1, 141.6, 136.3, 128.2, 128.1, 127.0, 125.9, 124.4, 116.8, 113.7, 103.0, 62.8, 55.2, 53.5, 42.4; HRMS ($FAB^+$) calcd for $C_{24}H_{25}NO_3$ $[M + H]^+$ 376.1913, found *m*/*z* 376.1899; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 12.7 min (major) and 14.9 min (minor).

***trans*-3-(Diallylamino)-4-(4-fluorophenyl)-6-phenyl-3,4-dihydropyran-2-one (4g)**

Colorless crystals; $[\alpha]_D^{22}$ = +27 ° (*c* = 0.50 in $CHCl_3$, 92% ee); mp 68–69 °C; IR (ATR): ν = 2838, 1756, 1509, 1276, 1227, 1148, 1122, 1021 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 7.65–7.61 (m, 2H), 7.41–7.37 (m, 3H), 7.27–7.19 (m, 2H), 7.08–7.02 (m, 2H), 5.73 (d, *J* = 2.5 Hz, 1H), 5.51–5.36 (m, 2H), 5.07–4.99 (m, 4H), 3.98 (dd, *J* = 12.5 Hz, 2.5 Hz, 1H), 3.83 (d, *J* = 12.5 Hz, 1H), 3.49–3.32 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ = 167.7, 163.6, 160.0, 148.6, 137.2, 136.1, 131.8, 129.8, 129.7, 129.1, 128.4, 124.5, 117.1, 115.2, 114.9, 104.8, 62.8, 53.6, 41.9; Anal. Calcd for $C_{23}H_{22}FNO_2$: C, 76.01; H, 6.10; N, 3.85. Found: C, 75.95; H, 6.21; N, 3.82; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 7.3 min (major) and 9.2 min (minor).

***trans*-3-(Diallylamino)-6-(4-fluorophenyl)-4-phenyl-3,4-dihydropyran-2-one (4h)**

Colorless crystals; $[\alpha]_D^{20}$ = +38 ° (*c* = 0.50 in $CHCl_3$, 94% ee); mp 80–81 °C; IR (ATR): ν = 2843, 1754, 1600, 1508, 1279, 1234, 1148, 1108, 1033 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 7.62–7.56 (m, 2H), 7.38–7.21 (m, 5H), 7.08–7.02 (m, 2H), 5.70 (d, *J* = 2.3 Hz, 1H), 5.50–5.35 (m, 2H), 5.05–4.96 (m, 4H), 3.98 (dd, *J* = 12.4 Hz, 2.5 Hz, 1H), 3.88 (d, *J* = 12.4 Hz, 1H), 3.46–3.28 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ = 167.7, 164.9, 161.2, 147.6, 141.4, 136.2, 128.3, 127.2, 126.6, 126.5, 117.0, 115.6, 115.3, 104.7, 62.8, 53.6, 42.6; Anal. Calcd for $C_{23}H_{22}FNO_2$: C, 76.01; H, 6.10; N, 3.85. Found: C, 75.85; H, 6.21; N, 3.82; HPLC analysis:

DAICEL Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 8.6 min (major) and 10.1 min (minor).

***trans*-4-(4-Bromophenyl)-3-(diallylamino)- 6-phenyl-3,4-dihydropyran-2-one (4i)**

Colorless crystals; $[\alpha]_D^{19}$ = +19 ° (*c* = 0.50 in $CHCl_3$, 92% ee); mp 69–70 °C; IR (ATR): ν = 2843, 1768, 1485, 1283, 1136, 1106, 1071, 1034, 1020, 1008 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.63–7.59 (m, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.38–7.35 (m, 3H), 7.11 (d, *J* = 8.2 Hz, 2H), 5.70 (d, *J* = 2.1 Hz, 1H), 5.49–5.35 (m, 2H), 5.07–4.98 (m, 4H), 3.96 (dd, *J* = 12.4 Hz, 2.1 Hz, 1H), 3.83 (d, *J* = 12.4 Hz, 1H), 3.48–3.30 (m, 4H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 167.5, 148.8, 140.1, 136.1, 131.7, 131.3, 129.2, 128.4, 120.9, 117.2, 104.2, 62.6, 53.6, 42.1; Anal. Calcd for $C_{23}H_{22}NO_2Br$: C, 65.10; H, 5.23; N, 3.30. Found: C, 65.12; H, 5.35; N, 3.29; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 8.1 min (major) and 10.7 min (minor).

(3*R*,4*R*)**-6-(4-Bromophenyl)-3-(diallylamino)- 4-phenyl-3,4-dihydropyran-2-one (4j)**[12]

Colorless crystals; $[\alpha]_D^{19}$ = +37 ° (*c* = 0.50 in $CHCl_3$, 92% ee); mp 93–94 °C; IR (ATR): ν = 2838, 1761, 1484, 1267, 1149, 1116, 1073, 1031, 1002 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.53–7.46 (m, 4H), 7.39–7.21 (m, 5H), 5.78 (d, *J* = 2.3 Hz, 1H), 5.51–5.36 (m, 2H), 5.05–4.97 (m, 4H), 3.97 (dd, *J* = 12.5 Hz, 2.3 Hz, 1H), 3.89 (d, *J* = 12.5 Hz, 1H), 3.47–3.29 (m, 4H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 167.6, 147.6, 141.2, 136.2, 131.6, 130.8, 128.3, 128.2, 127.2, 126.1, 123.2, 117.0, 105.6, 62.7, 53.6, 42.6; Anal. Calcd for $C_{23}H_{22}NO_2Br$: C, 65.10; H, 5.23; N, 3.30. Found: C, 64.98; H, 5.00; N, 3.34; HPLC analysis: Chiralpak AD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 14.1 min (major) and 15.5 min (minor).

***trans*-4-(4-Bromophenyl)-3-(diallylamino)- 6-(4-methoxyphenyl)-3,4-dihydropyran-2-one (4k)**

Colorless oil; ; $[\alpha]_D^{16}$ = +12 ° (*c* = 0.50 in $CHCl_3$, 97% ee); IR (ATR): ν = 2838, 1761, 1608, 1511, 1283, 1247, 1177, 1139, 1108, 1074, 1024, 1008 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.54 (d, *J* = 8.9 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.56 (d, *J* = 2.1 Hz, 1H), 5.48–5.33 (m, 2H), 5.06–4.97 (m, 4H), 3.83–3.78 (m, 5H), 3.47–3.28 (m, 4H); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 167.7, 160.2, 148.5, 140.7, 136.1, 131.2, 130.0, 126.0, 124.2, 120.8, 117.1, 113.7, 102.3, 62.6, 55.3, 53.5, 42.0; HRMS ($FAB^+$) calcd for $C_{24}H_{24}NO_3Br$ $[M + H]^+$ 454.1018, found *m*/*z* 454.1034; HPLC analysis: Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 13.0 min (major) and 18.6 min (minor).

***trans*-6-(4-Bromophenyl)-3-(diallylamino)- 4-(4-methoxyphenyl)-3,4-dihydropyran-2-one (4l)**

Colorless oil; $[\alpha]_D^{18}$ = +30 ° (*c* = 0.50 in $CHCl_3$, 94% ee); IR (ATR): ν = 2837, 1763, 1511, 1487, 1248, 1177, 1107, 1073, 1032, 1005 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.52–7.45 (m, 4H), 7.13 (d, *J* = 8.6 Hz, 2H),

6.88 (d, $J$ = 8.6 Hz, 2H), 5.75 (d, $J$ = 2.3 Hz, 1H), 5.75–5.38 (m, 2H), 5.06–4.97 (m, 4H), 3.94–3.77 (m, 5H), 3.41–3.28 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ = 167.7, 158.7, 147.4, 136.3, 133.2, 131.6, 130.9, 129.2, 126.1, 123.1, 117.0, 113.7, 105.9, 62.7, 55.3, 53.6, 41.8; Anal. Calcd for $C_{23}H_{22}NO_2Br$: C, 63.44; H, 5.32; N, 3.08. Found: C, 63.44; H, 5.18; N, 3.02; HPLC analysis: Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 12.1 min (major) and 28.8 min (minor).

***trans*-3-(Diallylamino)-4-methyl-6-phenyl-3,4-dihydropyran-2-one (4m)**

Colorless oil; ; $[\alpha]_D^{17}$ = +65 ° ($c$ = 0.50 in $CHCl_3$, 67% ee); IR (ATR): ν = 2847, 1750, 1448, 1278, 11278, 1264, 1117, 1143, 1105, 1083, 1041, 1027 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 7.60–7.56 (m, 2H), 7.38–7.28 (m, 3H), 5.86–5.71 (m, 2H), 5.59 (d, $J$ = 2.2 Hz, 1H), 5.26–5.08 (m, 4H), 3.53–3.34 (m, 5H), 1.27 (d, $J$ = 6.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$): 168.5, 147.5, 136.8, 131.9, 128.7, 128.3, 124.3, 116.8, 106.7, 62.9, 53.8, 30.2, 19.0; Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.21; H, 7.58; N, 4.82; HPLC analysis: Chiralcel OD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 5.9 min (major) and 6.8 min (minor).

***trans*-3-(Diallylamino)-4-phenyl-6-[(*E*)-2-phenylvinyl]-3,4-dihydropyran-2-one (4n)**

Colorless crystals; $[\alpha]_D^{22}$ = +71 ° ($c$ = 0.50 in $CHCl_3$, 87% ee); mp 69–71 °C; IR (ATR): ν = 2818, 1753, 1642, 1449, 1264, 1140, 1125, 1058, 1032 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 7.45–7.19 (m, 10H), 7.13 (d, $J$ = 15.9 Hz, 1H), 6.46 (d, $J$ = 15.9 Hz, 1H), 5.49–5.34 (m, 2H), 5.33 (d, $J$ = 2.5 Hz, 1H), 5.05–4.95 (m, 4H), 3.94 (dd, $J$ = 12.5 Hz, 2.5 Hz, 1H), 3.84 (d, $J$ = 12.5 Hz, 1H), 3.46–3.27 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ = 167.7, 147.9, 141.3, 136.3, 136.0, 130.0, 128.6, 128.3, 128.2, 128.1, 127.1, 126.7, 119.6, 117.0, 109.6, 63.0, 53.6, 42.9; Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.73; H, 6.94; N, 3.71; HPLC analysis: Chiralpak AD-H, hexane/2-propanol = 60/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 11.9 min (major) and 14.2 min (minor).

## ACKNOWLEDGEMENTS

This study was supported in part by the Grant of the 21st Century COE Program from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We wish to thank Mr. Masakazu Nagasawa, Mr. Masahiko Bando, Dr. Yoshikazu Kawano and Mrs. Tomoko Shinohara (Otsuka Pharmaceutical Co., Ltd.) for their kind help with high resolution mass spectrometry, X-ray crystallographic analysis, and elemental analysis. We would also like to thank Dr. Takashi Tozawa (Mitsubishi Pharma Corporation) for helpful discussion.

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12. The product **4j** was recrystallized from hexane/$Et_2O$. Crystal data: $C_{23}H_{22}NO_2Br$ (FW = 424.34), orthorhombic, $P2_12_12_1$, $a$ = 12.337(6) Å, $b$ = 20.477(4) Å, $c$ = 8.382(4) Å, $V$ = 2117(1) Å$^3$, $Z$ = 4.0, $D_{calcd}$ = 1.331g cm$^{-3}$, $T$ = 295 K. X-Ray intensities were measured on a Rigaku AFC-5S diffractometer with graphite-monochromated Mo $K\alpha$ radiation ($\lambda$ = 0.710690 Å). The final $R$ factors was 0.043 ($R$w = 0.098 for all data) for 1989 reflections with $I > 2\sigma(I)$.
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